Attorney Docket: 4555US

IN THE SPECIFICATION:

Please note that amendments to the specification are shown below in clean form. A marked up version of the amendments is attached.

Please amend the paragraph beginning at page 2, line 7 to read as follows:

Technical Field: The invention relates to CD40 binding proteins, which can be used as modulators of the CD40 signaling pathway and/or the CD40-induced nuclear factor kappa B (NF-κB) activating pathway and thus useful in the treatment of CD40 related diseases (*e.g.*, inflammatory diseases) and/or NF-kB related diseases and/or in the improvement of anti-tumor treatments. The current invention also relates to nucleic acid sequences coding for the CD40 interacting proteins (also called "TTRAP" ("TRAF and TNF receptor associated protein") for CD40 receptor associated protein). The invention further relates to the use of the polypeptides derived from these CD40 interacting proteins in the treatment of CD40 and/or NF-kB related diseases and/or cancer. Furthermore, the invention concerns pharmaceutical preparations comprising the CD40 interacting proteins or polypeptides derived from these proteins.

Please amend the paragraph beginning at page 2, line 17 to read as follows:

Background: CD40 is a receptor of the tumor necrosis factor ("TNF") - receptor superfamily (Banchereau *et al.*, 1994), which is expressed at the surface of B-cells, antigen presenting cells (APC), and several non-hematopoietic cells such as endothelial cells (Hollenbaugh *et al.*, 1995), epithelial cells (Galy & Spits, 1992), fibroblasts (Fries *et al.*, 1995) and keratinocytes (Gaspari *et al.*, 1996). The ligand for CD40 (CD40L) occurs mainly on activated T-cells. Up to now the role of CD40 was mainly studied in the context of the T-cell APC/B-cell interaction (for a review, see Noelle, 1996). Amongst others, the CD40-CD40L interaction seems to be important for the T-cell mediated immunity and for primary and secondary humoral immune response. These findings were confirmed by experiments in mouse models showing that treatment with anti-CD40L antibodies resulted in blocking of the development of mouse



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equivalents of human autoimmune diseases such as arthritis (Durie et al. 1993), oophoritis (Griggs et al., 1996) and multiple sclerosis (Gerritse et al., 1996).

Please amend the paragraph beginning at page 4, line 8 to read as follows:

The invention also includes an isolated functional protein either comprising an amino acid sequence with 70-100% homology to the amino acid sequence depicted in SEQ ID NO: 2 or either comprising an amino acid sequence with 70-100% homology to the amino acid sequence depicted in SEQ ID NO: 4 or in the alternative comprising an amino acid sequence with 70-100% homology to the amino acid sequence depicted in SEQ ID NO: 6.

Please amend the paragraph beginning at page 4, line 13 to read as follows:

More specifically, the functional protein comprises an amino acid sequence with 70-100% homology to the amino acids 54-362 of SEQ ID NO: 2, even more specifically the functional protein comprises an amino acid sequence with 70-100% homology to the amino acids 274-362 of SEQ ID NO: 2 or in the alternative and/or comprising an amino acid sequence with 70-100% homology to the amino acids 2-245 of SEQ ID NO: 6.

Please amend the paragraph beginning at page 4, line 18 to read as follows:

Furthermore, the invention also includes those proteins or peptides having 70-100% homology to, at least, any of the three peptides as depicted in SEQ ID NO: 2 located between the residues 115-121, 145-153 and 347-352 respectively. The amino acid sequence of residue numbering 115-121 is SLITWNI; the amino acid sequence of residue numbering 145-153 is PDVIFLQEV and the amino acid sequence of residue numbering 347-352 is FPSDHW.

Please amend the paragraph beginning at page 5, line 17 to read as follows:



One embodiment of the invention is a protein with SEQ ID NO: 2. Another embodiment of the invention is a protein with SEQ ID NO: 4. A further embodiment of the invention concerns a protein with SEQ ID NO: 6.

Please amend the paragraph beginning at page 7, line 16 to read as follows:



Another aspect of the invention involves DNA molecules, also called nucleic acid sequences, encoding for the aforementioned proteins, preferably a nucleic acid sequence with 70-100% homology to the DNA sequence depicted in SEQ ID NO: 1 and/or a nucleic acid sequence with 70-100% homology to the DNA sequence depicted in SEQ ID NO: 3 or in the alternative a nucleic acid sequence with 70-100% homology to the DNA sequence depicted in SEQ ID NO: 5.

Please amend the paragraph beginning at page 16, line 8 to read as follows:



"Compound" means any chemical or biological compound, including simple or complex inorganic or organic molecules, peptides, peptido-mimetics, proteins, antibodies, carbohydrates or nucleic acids, that interferes with the interaction of a protein depicted in SEQ ID NO: 2, SEQ ID NO: 4, or SEQ ID NO: 6 with a compound of the CD40 and/or NF-kB related pathway.

Please amend the paragraph beginning at page 16, line 25 to read as follows:



The functional protein of the invention is administered at a concentration that is therapeutically effective to prevent allograft rejection, graft versus host disease ("GVHD"), allergy and autoimmune diseases. The dosage and mode of administration will depend on the individual. Generally, the compositions are administered so that the functional protein is given at a dose between 1 mg/kg and 10 mg/kg, more preferably between 10 mg/kg and 5 mg/kg, most preferably between 0.1 and 2 mg/kg. Preferably, it is given as a bolus dose. Continuous short time infusion (during 30 minutes) may also be used. The compositions comprising the functional protein according to the invention may be infused at a dose between 5 and 20 mg/kg/minute, more preferably between 7 and 15 mg/kg/minute.

Please amend the paragraph beginning at page 17, line 10 to read as follows:

With regard to the use of the functional protein of the present invention to prevent allograft rejection, it should be stressed that the proteins of the present invention or the compositions comprising the same may be administered before, during or after the organ transplantation as is desired from case to case. In case the protein or the compositions comprising the same are administered directly to the host, treatment will preferably start at the time of the transplantation and continue afterwards in order to prevent the activation and differentiation of host T cells against the major histocompatibility complex ("MHC") on the allograft. In case the donor organ is *ex vivo* perfused with the functional protein according to the invention or the compositions comprising the same, treatment of the donor organ ex vivo will start before the time of the transplantation of the donor organ in order to prevent the activation and differentiation of host T cells against the MHC on the allograft

Please amend the paragraph beginning at page 19, line 2 to read as follows:

Full length human TTRAP cDNA was obtained by screening a HUVEC cDNA library with the TTRAP fragment as probe. A cDNA of about 2 kb was isolated, with an open reading frame of 1086 nucleotides encoding for a protein of 362 amino acids (SEQ ID NO: 2).

Please amend the paragraph beginning at page 19, line 5 to read as follows:

The mouse TTRAP homologue was obtained by screening the EST database and aligning the homologous sequences. Human and mouse TTRAP are approximately 65% identical and 70% similar on the amino acid level. The mouse sequence is shown in SEQ ID NO: 3.

Please amend the paragraph beginning at page 19, line 9 to read as follows:

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Nucleotide sequence analysis was carried out using dye terminator mix and a 310 Genetic analyzer from Perkin Elmer. The nucleotide sequence of TTRAP is shown in SEQ ID NO:1 whereas the sequence of 4C4 is shown in SEQ ID NO: 5.

Please amend the paragraph beginning at page 21, line 13 to read as follows:

D'1

4C4 protein is interacting with CD40, CD30, TNF-RII, with the longest fragment of TTRAP and with a deletion mutant of TRAF3 which still contains the largest part of the TRAF domain (from aa 380 to the carboxy terminal end of the protein. A smaller form of 4C4 (from amino acid 2 - amino acid 245 in SEQ ID NO: 6) is also capable to interact with CD40.

Please amend the paragraph beginning at page 25, line 20 to read as follows:

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Fas and CD40 are both members of the TNF-Receptor superfamily. DAXX was originally isolated as a Fas-binding protein, in a yeast two-hybrid screen (Yang et al., Cell, 89, 1067-76, 1997). The protein was shown to interact specifically with the death domain of Fas. It was reported to play a role in apoptosis via the activation of the Jun N-terminal kinase. The authors examined the binding of a partial clone of human DAXX (from amino acid 501 till the end) to the cytoplasmic tail of mouse CD40, and could not detect interaction. In addition, an *in vitro* interaction assay of full length DAXX with glutothione S-tranferase-CD40 ("GST-CD40") also turned out to be negative. Therefore, the authors conclude that DAXX does not associate with CD40.